In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

The Examiner has asserted that Southern et al. teaches a method for sequencing DNA comprising all of the features of claim 21. The Examiner has acknowledged that Southern et al. does not teach the feature where a heterogeneous population of single-stranded DNA is immobilized in a unique amount in the same reaction zone. The Examiner has asserted that Bensimon et al. discloses this feature.

The key difference between the present invention and the disclosure of Southern et al. is that the present method of sequencing DNA allows a heterogeneous population of

single stranded DNAs to be sequenced when they are immobilized in a unique amount in the same reaction zone.

Contrary to the Examiner's assertion, Bensimon et al. does not teach a method wherein a heterogeneous population of a single stranded DNA is immobilized in a unique amount in the same reaction zone. In fact, Bensimon et al. describes the use of atomic force (AFM) microscopy for sequencing DNA. This method requires that an individual double stranded nucleic acid is attached to the AFM device, which comprises a movable lever close to the sample surface. One strand of the DNA molecule is attached to the sample surface and one strand is attached to the movable lever. The energy required to move the lever, and thereby separate the strands, can be used to determine the sequence of the nucleic acid molecule.

The nucleic acid molecules of Bensimon et al. are not immobilized in the same reaction zone. It is clear from Bensimon et al. that only one sequence at a time can be analyzed in the AFM device. Column 7, lines 27-30, of Bensimon et al. states that the heterogeneous population of DNA molecules are tested in series, by coupling them one after another to the measuring surface. Therefore, the DNA molecules are coupled to the surface at separate locations, so that they can be individually sequenced in separate steps. In contrast, step (a) of claim 21 of the present invention requires that each of the single stranded DNAs is immobilized in the same reaction zone, such that the sequence of each of the DNAs in the population can be determined together in the same reaction steps (b) to (g). Thus, in certain embodiments of the present invention, the sequence of each of the

DNA may be determined simultaneously. The DNA molecules of Bensimon et al. are not immobilized in the same reaction zone according to claim 21 of the present invention because the sequence of the DNAs is not determined together in the same reaction step or series of steps.

Moreover, there is no suggestion or incentive to motivate the skilled artisan to combine the teaching of Bensimon et al. with Southern et al. as the techniques involved in the references are wholly unrelated to each other. The methods of Southern et al. are dependent on a series of chemical and enzymatic steps. In contrast, the method of Bensimon et al. utilizes a physical method of measuring the base pairing energy. Further, the method of Bensimon et al., which involves the immobilization of a number of DNA molecules on a solid support, is particularly adapted to the use of this physical method. The DNA molecules are only immobilized on the solid surface in Bensimon et al. in order to allow them to be attached to the AFM device so that their strands are separated. There is no suggestion whatsoever in Bensimon et al. that there is any particular advantage associated with immobilizing a population of heterogeneous DNA molecules in any particular way which may be transferable to a chemical or enzymatic method of DNA sequencing. The "express advantages," which the Examiner suggests are noted by Bensimon et al. in relation to their method, do not result solely from an independent feature of immobilizing a heterogeneous population of DNAs on a solid support, but only from doing so in the context of atomic force microscopy. Therefore, one of ordinary skill in the

art would not be motivated to combine the teachings of Southern et al. with that of Bensimon et al.

Therefore, because there is no suggestion or incentive to motivate a skilled artisan to modify or combine references and because the references, singly or in combination, fail to teach each and every limitation of the claims, Applicants respectfully request withdrawal of the rejection of claims 21-32 under 35 U.S.C. § 103(a).

Claims 21-25 and 27-32 have been rejected under 35 U.S.C. § 103(a) over Macevicz et al. (PCT Publication No. WO 96/33205) in view of Bensimon et al. Applicants respectfully traverse this rejection.

The Examiner has asserted that Macevicz et al. teaches a method for sequencing DNA comprising all of the features of claim 21. The Examiner has acknowledged that Macevicz et al. does not teach the feature where a heterogeneous population of single-stranded DNA is immobilized in a unique amount in the same reaction zone. The Examiner has asserted that Bensimon et al. discloses this feature.

The key difference between the present invention and the disclosure of Macevicz et al. is that the present method of sequencing DNA allows a heterogeneous population of single stranded DNAs to be sequenced when they are immobilized in a unique amount in the same reaction zone.

As discussed above, Bensimon et al. does not teach a method wherein a heterogeneous population of a single stranded DNA is immobilized in a unique amount in the same reaction zone.

Moreover, there is no suggestion or incentive to motivate the skilled artisan to combine the teaching of Bensimon et al. with Macevicz et al. as the techniques involved in the references are wholly unrelated to each other. The methods of Macevicz et al. are dependent on a series of chemical and enzymatic steps. In contrast, the method of Bensimon et al. utilizes a physical method of measuring the base pairing energy. Further, the method of Bensimon et al., which involves the immobilization of a number of DNA molecules on a solid support, is particularly adapted to the use of this physical method. The DNA molecules are only immobilized on the solid surface in Bensimon et al. in order to allow them to be attached to the AFM device so that their strands are separated. As noted above, there is no suggestion whatsoever in Bensimon et al. that there is any particular advantage associated with immobilizing a population of heterogeneous DNA molecules in any particular way which may be transferable to a chemical or enzymatic method of DNA sequencing. Again, the "express advantages," which the Examiner suggests are noted by Bensimon et al. in relation to their method, do not result solely from an independent feature of immobilizaing a heterogeneous population of DNAs on a solid support, but only from doing so in the context of atomic force microscopy. Therefore, one of ordinary skill in the art would not be motivated to combine the teachings of Macevicz et al. with that of Bensimon et al.

Therefore, because there is no suggestion or incentive to motivate a skilled artisan to modify or combine references and because the references, singly or in combination, fail

to teach each and every limitation of the claims, Applicants respectfully request withdrawal of the rejection of claims 21-25 and 27-32 under 35 U.S.C. § 103(a).

Claims 21-39 and 41-43 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. in view of Bensimon et al. and further in view of Stratagene Catalog (1988, page 39). Applicants respectfully traverse this rejection.

The Examiner has stated that Southern et al. in view of Bensimon et al. teaches the method of claims 21-32. The Examiner acknowledges that Southern et al. and Bensimon et al. provide no motivation to combine all the reagents for identifying a base at a target position in a single-stranded sample DNA sequence in the form of a kit.

The reasons why the combination of Southern et al. and Bensimon et al. does not render the claimed invention obvious are discussed in detail above.

Briefly, the key difference between the present invention and the disclosure of Southern et al. is that Southern et al. does not teach a method of sequencing DNA where a heterogeneous population of single stranded DNAs to be sequenced are immobilized in a unique amount in the same reaction zone. This deficiency in Southern et al. cannot be remedied by the teachings of Bensimon et al. As mentioned above, Bensimon et al. does not teach a method wherein a heterogeneous population of a single stranded DNA is immobilized in a unique amount in the same reaction zone. In fact, Bensimon et al. describes the use of atomic force (AFM) microscopy for sequencing DNA.

The DNA molecules of Bensimon et al. are not immobilized in the same reaction zone according to claim 21 of the present invention because the sequence of the DNAs is

not determined together in the same reaction step or series of steps. It is clear from Bensimon et al. that only one sequence at a time can be analyzed in the AFM device. Therefore, the DNA molecules are coupled to the surface at separate locations, so that they can be individually sequenced in separate steps.

Moreover, there is no suggestion or incentive to motivate the skilled artisan to combine the teaching of Bensimon et al. with Southern et al. as the techniques involved in the references are wholly unrelated to each other. The methods of Southern et al. are dependent on a series of chemical and enzymatic steps. In contrast, the method of Bensimon et al. utilizes a physical method of measuring the base pairing energy. The DNA molecules are only immobilized on the solid surface in Bensimon et al. in order to allow them to be attached to the AFM device so that their strands are separated. Therefore, one of ordinary skill in the art would not be motivated to combine the teachings of Southern et al. with that of Bensimon et al.

Further, the combination of Southern et al. with Bensimon et al. and the Stratagene Catalog also fail to rendered claims 21-39 and 41-43 of the present invention obvious.

Therefore, because there is no suggestion or incentive to motivate a skilled artisan to modify or combine references and because the references, singly or in combination, fail to teach each and every limitation of the claims, Applicants respectfully request withdrawal of the rejection of claims 21-39 and 41-43 under 35 U.S.C. § 103(a).

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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